IMMUNOBIOLOGICAL PROPERTIES OF THE SERUM IN MULTIPLE SCLEROSIS

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Serum of patients with multiple sclerosis, when injected into guinea pigs, inhibits the development of experimental allergic encephalomyelitis in these animals. The protective effect depends on the dose of serum.

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Reports in the literature describe the immunobiological properties of serum in demyelinating diseases of nerve tissue. For example, serum of patients with multiple sclerosis (MS) have been shown to possess a gliotoxic and demyelinating action in brain tissue cultures [3, 4, 7].

In experimental allergic encephalomyelitis (EAE), a model of human demyelinating diseases, besides the harmful action of serum in vitro [4, 7], a marked protective effect of brain antiserum has been observed on the intact organism [2, 6, 8].

The object of the present investigation was to study the immunobiological protective properties of the serum in MS.

EXPERIMENTAL METHOD

The sera of 40 patients with MS admitted for treatment to the Institute of Neurology, Academy of Medical Sciences of the USSR, were investigated. All these patients had the typical clinical picture of MS, including lesions of the cerebellar, pyramidal, and visual systems. The disease followed a remittent or chronic progressive course.

The scheme of the investigations was as follows. Sera, obtained under sterile conditions from patients with MS, were injected intravenously into intact guinea pigs (recipients) in a dose of 2 ml 24 h before reproduction of EAE by a single intradermal sensitization with brain tissue suspension from a healthy monkey mixed with Freund's adjuvant. Altogether each recipient received 10 ml serum in 5 injections, given over a period of 5 days after sensitization.

Serum of patients with MS and of the recipient animals was tested for its content of brain antibodies by the complement fixation reaction in the cold. Meanwhile, skin reactions of delayed type in the guinea pigs were studied with brain tissue antigens [1].

The pathohistologic investigation included staining of brain sections with hematoxylin-eosin and by the methods of Nissl, Spielmeyer, Feulgen, and Brachet.

This paper describes the results of 5 series of experiments carried out on 64 male guinea pigs weighing 350-450 g.

EXPERIMENTAL RESULTS

The results of the clinical, immunologic, and morphological investigations of the experimental and control animals are given in Table 1.

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TABLE 1. Immunologic Properties of Serum in Multiple Sclerosis

Series no.	No. of animals	Characteristics of serum injected	Dose of serum injected (in ml)	Interval between injection of serum and of encephalitogenic material (in h)	Injection of encephalitogenic material	No. of animals with neurological manifestations of EAE	Mean titer of brain antibodies	Diam. of skin reaction (in mm)	Intensity of pathomorphological changes
I	10	–	–	–	+	9	1:800	15	+++
II	22	Serum of patients with MS	10	24	+	1	1:150	7	+
III	12	The same	3	24	+	10	1:600	15	+++
IV	10	" "	10	–	–	0	1:10	–	–
V	10	Serum of healthy persons	10	24	+	7	1:600	15	+++

*A 20% saline suspension of brain tissue (protein content 7-9 mg/ml by the micro-Kjeldahl method) from patients dying of multiple sclerosis and of guinea pigs with neurological manifestations of EAE, in a dilution of 1:10,000, was used as antigen for the complement fixation reaction.

After a single intradermal injection of encephalitogenic material into guinea pigs, the typical picture of EAE with characteristic neurological, immunologic, and morphological manifestations developed in 90% of cases (experiments of series I).

Intravenous injections of serum of patients with MS essentially modified the reactions of the recipients to subsequent injections of encephalitogenic material: in the experiments of series II, of 22 animals receiving 10 ml of serum from patients with MS, only one showed neurological manifestations of encephalomyelitis, including progressive loss of weight, spastic paralysis of the hind limbs, and disturbances of function of the pelvic organs. It is interesting to note that moderate skin reactions of delayed type were observed in clinically healthy recipients,and complement-fixing antibodies against brain tissue antigens used for sensitization were found in their serum. However, the severity of the changes in allergic reactivity (skin reactions and serum antibodies) in the recipients of the experiments of series II was much lower than in animals with the neurological picture of encephalomyelitis in series I.

Pathohistologic investigation of the brain tissue of animals with neurological manifestations showed well marked perivascular histiocytic and lymphocytic infiltration, proliferation of glial cells, and demyelination, scattered diffusely in the white matter and meninges. These changes in recipients without neurological manifestations were very slight in degree and affected mainly the white matter surrounding the ventricles.

Hence, injection of 10 ml serum of patients with MS caused a state of increased resistance of the recipients to the subsequent action of the encephalitogenic factor, manifested by a marked decrease in the incidence of EAE, lowering of the titer of serum brain antibodies, and a decrease in the intensity of the skin reactions and pathomorphological processes in nerve tissue.

After injection of serum of patients with MS in a dose not exceeding 3 ml (experiments of series III), resistance to encephalomyelitis was absent. Ten of the 12 animals of this series showed the typical neurological picture of encephalomyelitis.

In the experiments of series IV, following injection of 10 ml serum of patients with MS without subsequent reproduction of EAE (control of cytotoxic action of heterologous serum), neither neurological changes, serum antibodies, nor positive skin reactions were observed in the recipients.

In series V, in which serum of healthy persons was injected, a clinical picture of encephalomyelitis was observed in 7 of the 10 recipients (control of specificity of action of serum from patients with MS).

Analysis of the results showed that after injection of serum of patients with MS into guinea pigs, marked resistance to the subsequent action of encephalitogenic factor develops in the recipients. Induced resistance against encephalomyelitis is directly dependent on the dose of serum injected, and it is specific, as confirmed by the absence of a positive effect after injection of normal human serum. It should be emphasized that the specificity demonstrated is of a distinct organ character.

As regards the possible mechanism of resistance to encephalomyelitis, the most logical suggestion is that the immune organ-specific factor discovered in the serum of patients with MS is connected with humoral brain antibodies. These antibodies, in all probability, neutralize the encephalitogenic factor circulating in the blood stream, preventing it from penetrating into nerve tissue or acting as blocking antibodies. Another possible explanation of the increased resistance to encephalomyelitis is based on the assumption that the serum of patients with MS causes exhaustion of the immunologic apparatus as a result of elimination of cell clones specifically sensitive to brain tissue antigens [5].

The results of this investigation thus showed that injection of large doses of serum from patients with MS not only fails to produce characteristic lesions of nerve tissue in intact guinea pigs, but on the contrary prevents the development of allergic encephalomyelitis.

The fact that serum from patients with MS lowers specific sensitivity to the action of encephalitogenic factor is evidence of the existence of common pathogenetic mechanisms in MS and EAE, and demonstrates once more the dominant role of the allergic component in demyelinating lesions of nerve tissue.

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